REMARKS/ARGUMENTS

Claims 20-27 are pending in the above-referenced patent application and are currently under examination. In order to expedite prosecution, Applicants have amended claims 20 and 21 to pursue more focused subject matter. Support for the amendments to claims 20 and 21 can be found throughout the specification as filed. As such, no new matter has been introduced with the amendments to claims 20 and 21. Reconsideration is respectfully requested.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claim 20-27 stand rejected under 35 U.S.C. § 112, first paragraph, because the Office Action alleges that the specification, while being enabling for "using reversine (Compound A) to induce dedifferentiation of murine C2C12 myoblasts into multipotent stem cells losing the myogenic specific markers MyoD and myosin and differentiation of said multipotent stem cells into osteoblasts and adipocytes by using ODM and ADM, does not reasonably provide enablement for dedifferentiating various mesenchymal lineage committed mammalian cells into various or unknown multipotent stem cells, which can be differentiated into any cell type" (*see*, page 2 of the Office Action). Specifically, the Office Action alleges that "the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention without undue experimentation."

Applicants respectfully traverse this basis of rejection.

As an initial point, Applicants, without acquiescing to the merits of the rejection, have amended claim 20 to recite a method of identifying compounds that induce dedifferentiation of mesenchymal lineage committed mammalian cells into multipotent mesenchymal stem cells, wherein the mesenchymal lineage committed cells are selected from osteoblasts, myoblasts, chondrocytes, and adipocytes; wherein the mesenchymal lineage committed mammalian cells that have been contacted with the test compound are differentiated into different first and second mesenchymal lineage cell types that are selected from osteoblasts, myoblasts, chondrocytes, and adipocytes; and wherein the mesenchymal lineage committed cells are different cell types compared to the first and second mesenchymal lineage cell types.

Support for these amendments can be found throughout the specification as filed (*see*, for example, paragraphs 2, 40-41, 90, and 112 of U.S. Patent Publication No. 2007/0254884). Thus, no new matter is introduced by way of this amendment.

The Office Action alleges that the state of the art of dedifferentiation of mesenchymal lineage committed mammalian cells only shows dedifferentiation of muscle cells by reversine into multipotent stem cells that can be differentiated into osteoblasts, adipocytes, or chondrocytes. Applicants respectfully disagree.

Applicants respectfully submit that the instant claims are screening claims, directed to the identification of a dedifferentiation agent. Applicants submit that application of the screening method to C2C12 cells resulted in the identification of reversine as an agent capable of dedifferentiating myoblasts into multipotent mesenchymal stem cells. As explained below, Applicants submit that one having skill in the art would not engage in any undue experimentation in extrapolating Applicants' results to the presently claimed genus.

Accordingly, Applicants submit that the specification in combination with the teachings of the art amply enable the presently claimed methods. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.").

The Examiner has incorrectly determined that human annulus fibrosus cells and dermal fibroblasts are muscle cells or, could be muscle cells (*see*, page 5 of the Office Action mailed 6/3/2010). In contrast, Applicants respectfully submit that human annulus fibrosus cells are not muscle cells, but are adherent fibroblastic cells exhibiting an elongated morphology that expresses high levels of collagen type I and fibromodulin (*see*, page 2, second paragraph, of Saraiya *et al.*, a copy of which was previously submitted together with the Amendment filed on April 19, 2010). A myoblast is a mononucleated, undifferentiated muscle precursor cell and a fibroblast is a connective tissue cell that secretes extracellular matrix rich in collagen and other macromolecules. (See online Glossary of Molecular Biology of the Cell, 4th Edition, Alberts *et al.*; maintained at the National Center for Biotechnology Information, at

http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=mboc4&part=A4754#A5505, a copy of which is attached. Accordingly, one having skill in the art would not classify a fibroblast as a myoblast or muscle cell.

In addition, Applicants previously stated in the Amendment filed in the U.S. Patent and Trademark Office on April 19, 2010 that: Saraiya *et al.*, 2010, demonstrate that treatment of mesenchymal lineage committed human annulus fibrosus cells with reversine induces the cells to become multipotent stem cells that can differentiate into osteogenic cells, adipogenic cells, and chondrogenic cells; that Fania *et al.*, 2009, demonstrate that treatment of murine dermal fibroblasts with reversine induces the cells to become multipotent stem cells that can differentiate into skeletal muscle, smooth muscle, and bone cells; and that Applicants (Chen *et al.*, 2007, a copy of which is attached) provide post-filing data that shows that both murine 3T3E1 osteoblasts and human primary skeletal myoblasts treated with reversine can each differentiate into both osteogenic and adipogenic cells. Thus, Applicants have provided examples of dedifferentiating lineage committed stem cells such as murine myoblasts, murine osteoblasts, murine dermal fibroblasts, human annulus fibrosus cells, and human skeletal myoblasts treated with reversine can be differentiated into osteogenic cells, chondrogenic cells, adipogenic cells, and myogenic cells.

In view of the foregoing, Applicants submit that one having skill in the art would not engage in any undue experimentation in practicing the presently claimed invention wherein the lineage committed cells and the first and second mesenchymal cell types are selected from the group consisting of: osteoblasts, myoblasts, chondrocytes, and adipocytes. Applicants respectfully submit that as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). See M.P.E.P. § 2164.01(b).

The Office Action further alleges that the specification fails to provide adequate guidance and evidence for what kind of multipotent stem cells can be obtained from

dedifferentiation of various mesenchymal lineage committed cells. Applicants respectfully disagree.

The Examiner alleges that the claims only require exposing a test compound to the mesenchymal lineage committed mammalian cells but are silent about whether multipotent stem cells are generated or not and what kind of multipotent stem cells are generated. The Examiner further alleges that if there are no multipotent stem cells generated, then, there is no "dedifferentiation" of the mesenchymal lineage committed mammalian cells and it could be "transdifferentiation" of the mesenchymal lineage committed mammalian cells into the first and second cell types. Applicants respectfully note that the claims have been amended to recite multipotent mesenchymal stem cells and wherein the stem cells are differentiated into two different types of mesenchymal lineage cell types, *i.e.*, osteoblasts, myoblasts, chondrocytes, and adipocytes. Applicants respectfully submit that the claims recite that induction of differentiation of the cells contacted with the test compound into both the first cell type and the second cell type identifies the test compound as a compound that induces dedifferentiation of mesenchymal lineage committed mammalian cells. Applicants submit that the putative multipotent mesenchymal stem cells are tested for their capacity to differentiate into the first and second cell types in the absence of the test compound.

Accordingly, Applicants submit that if the contacted cells differentiate into the first and second mesenchymal cell types, they are multipotent mesenchymal stem cells, and thus, the test compound is identified as a compound capable of dedifferentiation of mesenchymal lineage committed mammalian cells into multipotent mesenchymal stem cells.

Further, Applicants submit that if the contacted cells fail to differentiate into the first and second mesenchymal cell types, they are not multipotent mesenchymal stem cells, and thus, the test compound is not capable of dedifferentiation of mesenchymal lineage committed mammalian cells into multipotent mesenchymal stem cells.

Applicants further submit that the skilled artisan would not mistake transdifferentiation for an agent that is not capable of inducing dedifferentiation. For example, because the cells contacted with the test compound are differentiated **in the absence of the test**

compound, the compound cannot be responsible for transdifferentiation. Accordingly, any transdifferentiation must be due to the ADM or ODM; however, this is not plausible because if the ODM and ADM induced transdifferentiation, then all cells, whether contacted or not with a test compound, would transdifferentiate, which is clearly not the case.

Thus, as explained in detail above, the ability of the cell contacted with the test compound to differentiate into two different mesenchymal cell types identifies the contacted cell as a multipotent mesenchymal stem cell.

The Examiner further alleges that the specification fails to provide adequate guidance and evidence for what kind of multipotent stem cells can be obtained from dedifferentiation of various mesenchymal lineage committed cells from numerous different mammals and how to identify numerous different cell types differentiated from said multipotent stem cells derived from various mammals. Applicants respectfully disagree.

The Examiner alleges the cell markers for multipotent stem cells and for differentiated mammalian cells differ among different cell types and different mammalian species. The Examiner uses comparative studies in human and mouse embryonic stem cells to support this argument. Applicants respectfully submit that the Examiner's arguments with regard to embryonic stem cells, which are **pluripotent stem cells**, are not relevant to the presently claimed **multipotent mesenchymal stem cells** or **mesenchymal lineage committed cells**. As noted in the previous Office Action, pluripotent cells have the ability to form all lineages of the body or soma (*i.e.*, the embryo proper). For example, an embryonic stem cell is a type of pluripotent stem cell that is able to form cells from each of the three germs layers, the ectoderm, the mesoderm, and the endoderm, but not extraembryonic cells. Pluripotency is often tested using teratoma formation assays or *in vitro* embryoid body formation assays. These assays allow the artisan to determine whether the cells are truly pluripotent, *i.e.*, capable of forming all lineages of the body or soma. The fact that not all embryonic stem cells share identical gene expression profiles or methylation patterns is not necessarily the determinative factor in accessing their pluripotentiality; if the stem cell forms cells of each of the three germ layers, it is pluripotent.

In contrast, a mesenchymal stem cell has the ability to form multiple cell types of one lineage. For example, mesenchymal stem cells are capable of forming cells of the mesenchymal cell lineage, for example, osteoblasts, myoblasts, chondrocytes, and adipocytes. It is not necessary, and would be unreasonable to assume, that mesenchymal lineage committed cells, such as osteoblasts, myoblasts, chondrocytes, and adipocytes, are identical across *mammalia*. However, Applicants submit that one having skill in the art can nevertheless identify osteoblasts, myoblasts, chondrocytes, and adipocytes across *mammalia*, because each cell type shares inherent and evolutionarily conserved characteristics that define the particular cell type, and that can be identified regardless of the species of mammal. For example, osteoblasts can be identified based on osteocalcin or alkaline phosphatase expression and Alizarin Red staining; myoblasts can be identified based on myosin or MyoD expression; adipocytes can be identified by Oil Red O staining; and chondrocytes can be identified by the expression of type II collagen and Alcian Blue staining.

Moreover, one having ordinary skill in the art would not have any difficulty in identifying osteoblasts, myoblasts, chondrocytes, and adipocytes from various mammalian species based on histological and morphological characteristics. In fact, the as-filed specification, in paragraph [0111] lists a number of art recognized sources for the morphological characterization of various mesenchymal lineage committed cells such as osteoblasts, myoblasts, chondrocytes, and adipocytes, (*see, e.g.*, Albertine and Gee, J. Leuk. Biol. 59(5):631-8 (1996); Allsopp *et al.*, J. Immunol. Methods 1998 May; 214(1-2):175-86 (1998); Ashley *et al.*, Leuk. Res. 18(1):37-48 (1994); Ashley *et al.*, Leuk. Res. 17(10):873-82 (1993);. Boutonnat *et al.*, C. R. Acad. Sci. III 321(11):901-7 (1998); Boyd Cell Growth Differ. 4(9):777-84 (1993); Dell'Accio *et al.*, J. Orthop. Res. 21(1):123-31 (2003); Ford *et al.*, J.Surg.Res. 62(1):23-8 (1996); Haas *et al.*, Acta Histochem. 102 (3):273 -80 (2000); Horan *et al.*, Methods Cell Biol. 33:469-90 (1990); Khalaf *et al.*, J. Immunol. Methods 165(1):121-5 (1993); Melnicoff *et al.*, J. Leuk Biol. 43(5):387-97 (1988); Modo *et al.*, Neuroimage 17(2):803-11 (2002); Muirhead, Morphologie 85:27(2001); Parish, Immunol. Cell Biol. 77(6):499-508 (1999); Pierelli *et al.*, Methods Cell Biol. 64(1):153-70 (2001); Waters *et al.*, Cytometry 48(3):146-52 (2002); Yuan *et al.*,

Microvascular Res. 40:228-9 (1990); and U.S. Pat. Nos.: 6,387,326; 6,076,583; 5,700,346; 5,318,795; 4,792,521; 4,783,401; 4,762,701; and 4,859,584).

In addition, it should be noted that mesenchymal stem cells have a characteristic cell morphology, *e.g.*, small round cells having a large nucleus and small cytoplasmic space, which are features not characteristic of differentiated cell types such as osteoblasts, myoblasts, chondrocytes, and adipocytes. Moreover, mesenchymal stem cells are able to self-renew and differentiate into more than one mesenchymal lineage committed cell type, whereas mesenchymal lineage committed cell types possess a limited ability to proliferate and are determined to differentiate along their respective cell lineages.

Thus, one having skill in the art would not encounter undue experimentation in identifying mesenchymal lineage committed cells such as osteoblasts, myoblasts, chondrocytes, and adipocytes from a mammal or determining if the multipotent mesenchymal stem cell differentiates into a first and second cell type such as an osteoblast, myoblast, chondrocyte, or adipocyte. Moreover, if the mesenchymal lineage committed cell that is contacted with a test compound is able to differentiate into the first and second mesenchymal cell types, then one having skill in the art would appreciate that the test compound dedifferentiated the mesenchymal lineage committed cell to a multipotent mesenchymal stem cell.

Accordingly, in view of the guidance provided in the specification as filed, together with the knowledge of one having ordinary skill in the art, Applicants respectfully submit that the entire claimed breadth of the currently pending claims is enabled and that one having skill in the art would not encounter any undue experimentation in practicing the presently claimed invention.

Reconsideration and withdrawal of this basis for rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Further, the Commissioner is hereby authorized to charge any additional fees or credit any overpayment in connection with this paper to Deposit Account No. 20-1430.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

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